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That I am familiar with the German and English languages;

That I am capable of translating from German to English;

That the translation attached hereto is a true and accurate translation of German Application DE 30 22 337 A1 titled, "Preparations for Contraception and for Treatment of Gynecological Disorders."

By Melissa Stanford

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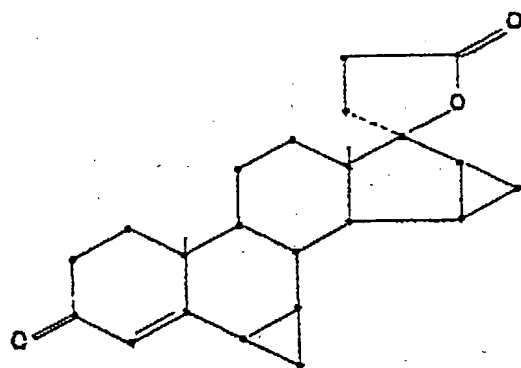
(71) Applicant: Schering AG Berlin and Bergkamen, 1000 Berlin,
DE

(72) Inventor: Eiger, Walter, Dr.; Beier, Sybille, B. S. Biol.;
Mannesmann, Gerda, Dr.; Schillinger, Ekkahard, Dr., 1000
Berlin, DE.

(54) Preparations for Contraception and for Treatment of
Gynecological Disorders

Claims

1. Preparations for contraception and for treatment of gynecological disorders based on 6 β ,7 β ; 15 β ,16 β -dimethylen-3-oxo-4-androstene- $\sqrt{17(\beta-1')}$ -spiro-5'7-perhydrofuran-2'-one of formula I



(I).

2. Preparations for contraception according to claim 1, characterized in that they additionally contain an estrogen.

3. Preparations for contraception according to claims 1 and 2, wherein they contain 0.5-50 mg of 6 β ,7 β ; 15 β ,16 β -dimethylene-3-oxo-4-androstene- $\sqrt{17(\beta-1')}$ -spiro-5'7-perhydrofuran-2'-one and 0.03-0.05 mg of 17 α -ethinyl-estradiol or a corresponding amount of another estrogen.

4. Preparations for treatment of gynecological disorders according to claim 1, wherein they contain 5-50 mg of 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene- $\sqrt{17(\beta-1')}$ -spiro-5'7-perhydrofuran-2'-one.

5. Process for the production of preparations for contraception and for treatment of gynecological disorders based on 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene- $\left[17(\beta-1')\right]$ -spiro-5,7-perhydrofuran-2'-one, wherein the active ingredient is processed in a way that is known in the art with vehicles, diluents and optionally flavoring correctives and converted into the ultimately desired method of administration.

6. Process for the production of preparations for contraception according to claim 5, wherein an estrogen is included as an additional active ingredient.

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Preparations for Contraception and for
Treatment of Gynecological Disorders

130061/0067

The invention relates to the subject that is characterized in the claims.

6 β ,7 β ;15 β ,16 β -Dimethylen-3-oxo-4-androstene- $\sqrt{17(\beta-1')}$ -spiro-5 $\sqrt{7}$ -perhydrofuran-2'-one is already known. The compound is described as a diuretic of the type of aldosterone antagonist in the example in German Laid-Open Specification 2 652 761.

It is known from "Journal of Clinical Endocrinology and Metabolism" 47 (3) 691-694 (1978) that the aldosterone antagonist spironolactone shows gestagenic action at a high dosage. In the modified Clauberg Test on infant female rabbits, a minimal action on the endometrium is found with 50 mg/kg/day of spironolactone. In the menstrual-period shift test on monkeys, 400 mg of spironolactone is required daily. In the case of little gestagenic action and the known side effects of spironolactone, use of this substance in hormonal contraception is not suitable.

It was now found, however, that 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene- $\sqrt{17(\beta-1')}$ -spiro-5 $\sqrt{7}$ -perhydrofuran-2'-one at dosages in which the antialdosterone action already occurs also has a considerable gestagenic action.

In the modified Clauberg Test, positive results are achieved after subcutaneous administration of the compound of formula I in rabbits with amounts of 0.1-1.0 mg. In the pregnancy maintenance test on rats and mice, the least amount required to achieve a positive effect is approximately 1-3 mg. In the receptor test, a strong binding to the gestagen receptor and only a very weak binding to the androgen receptor occur. It was also found that after oral administration of 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-

androstene- $\Delta^{17}(\beta-1')$ -spiro-5 Δ^7 -perhydrofuran-2'-one on male test subjects, the compound is bio-available.

6 β ,7 β ;15 β ,16 β -Dimethylen-3-oxo-4-androstene- $\Delta^{17}(\beta-1')$ -spiro-5 Δ^7 -perhydrofuran-2'-one can be used by itself or in combination with estrogens in preparations for contraception. According to the invention, the new preparations are to be used in women who desire contraception and suffer from high blood pressure or whose blood pressure increases when oral contraceptives are taken. Depending on the severity of the disease, the use according to the invention results in a reduction or even a normalization of the blood pressure values. In the cases in which the commonly used contraceptives have a negative effect on the blood pressure regulation, a more discrete increase in blood pressure can be avoided with the new preparations. Thus, this is the first time that the increases in blood pressure which are a danger in predisposed women in the case of hormonal contraception and which previously caused hormonal contraception to be discontinued are not observed. In contrast, the hormonal contraception is also made possible in patients with high pressure.

The natural corpus luteum progesterone -- but not its previously commonly used synthetic analogs -- has antimineral-corticoidal properties. With 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene- $\Delta^{17}(\beta-1')$ -spiro-5 Δ^7 -perhydrofuran-2'-one, a connection with a spectrum of activity that comes close to the progesterone is now available, which is also effective after oral administration.

As estrogens that are suitable for the agent for contraception according to the invention, the estrogens that are also commonly used to date are considered. In this case, the estrogen that is used should preferably be administered in doses such that the amount of estrogen that is used according to the invention is equal to that which corresponds to the administration of 0.03 to 0.05 mg of 17 α -ethinylestradiol. As estrogen components, i.a., the 17 α -ethinylestradiol ester and -ether, and, for example, ester of 17 α -ethinyl-7 α -methyl-1,3,5(10)-estratriene-1,3,17 β -triol (German Patent 1 593 509 and German Laid-Open Specification 2 818 164) are also suitable. As an estrogen component, 17 α -ethinylestradiol is preferred.

The dosage of the aldosterone antagonist with gestagenic action according to formula I is preferably to be 0.5-50 mg per day.

The estrogenic and gestagenic active ingredient components are preferably administered together orally; but they can also be administered separately and/or parenterally.

The daily dose is preferably administered one time. Preparations for contraception preferably contain 0.5-50 mg of 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene-[17(β -1')-spiro-5'7-perhydrofuran-2'-one and an amount of estrogen that corresponds to that of 0.03-0.05 mg of 17 α -ethinylestradiol, preferably 0.03-0.05 mg of 17 α -ethinylestradiol.

The aldosterone antagonist according to formula I can also be used in preparations for treating gynecological disorders. Because of the advantageous profile of action, 6 β ,7 β ;15 β ,16 β -

dimethylen-3-oxo-4-androstene- $\Delta^{17}(\beta-1')$ -spiro-5 Δ^7 -perhydrofuran-2'-one is especially well suited for treating premenstrual symptoms, such as headaches, depressive moods, water retention and mastodynia. The daily dose in the treatment of premenstrual symptoms is approximately 5-50 mg.

The formulation of the preparations according to the invention based on 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene- $\Delta^{17}(\beta-1')$ -spiro-5 Δ^7 -perhydrofuran-2'-one is carried out in a way that is known in the art, by the active ingredient, optionally in combination with an estrogen, being processed with the vehicles, diluents, optionally flavoring correctives, etc. that are commonly used in galenicals and being converted into the desired method of administration. For the preferred oral administration, especially tablets, coated tablets, capsules, pills, suspensions or solutions are suitable. For the parenteral administration, especially oily solutions, such as, for example, solutions in sesame oil, castor oil and cottonseed oil, are suitable. To increase solubility, solubilizers, such as, for example, benzyl benzoate or benzyl alcohol can be added.

Below, the formulation of several preparations based on various embodiments is explained in more detail.

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Example 1

20.0 mg of 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene- $\sqrt{17(\beta-1')}$ -spiro-5'7-perhydrofuran-2'-one and 0.05 mg of 17 α -ethinylestradiol are mixed homogeneously with 140.45 mg of lactose, 59.5 mg of corn starch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate and without prior granulation pressed into a table with a final weight of 225 mg.

Example 2

Analogously to Example 1, 10 mg of 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene- $\sqrt{17(\beta-1')}$ -spiro-5'7-perhydrofuran-2'-one and 0.05 mg of 17 α -ethinylestradiol with 150.45 mg of lactose, 59.5 mg of corn starch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate are pressed into tablets with a final weight of 225 mg.

Example 3

Analogously to Example 1, 20 mg of 6 β ,7 β ;15 β ,16 β -dimethylen-3-oxo-4-androstene- $\sqrt{17(\beta-1')}$ -spiro-5'7-perhydrofuran-2'-one with 140.5 mg of lactose, 59.5 mg of corn starch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate are pressed into tablets with a final weight of 225 mg.